Altered neural circuits in the primary motor cortex of hemi-Parkinsonian rats

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Parkinson's disease (PD) is the second most common debilitating neurologic disease after Alzheimer's disease globally. By local field potential (LFP) recording, we have detected alterations in the activities in the primary motor cortex, M1, of un-anesthetized, freely moving hemi-Parkinsonian rats. These alterations include the presence of exacerbated oscillations in the β-regime and the more frequent appearance of high-voltage-spindle (HVS) episodes. In addition, the local field potentials recorded from the L2/3 and L5 layers of the M1 of hemi-PD rats are anti-phase to one another and exhibit high coherence in the region between 30 and 40 Hz.

Deep-Brain-Stimulation (DBS) targeting at regions lying deep in the brain, such as the subthalamic nucleus (STN), has been used to treat patients with advanced PD. Application of high frequency stimulation, 130 Hz, on STN in hemi-Parkinsonian rats could also attenuate the β-oscillation and HVS, as well as reverse the amphetamine-induced rotation, which is a characteristic movement of these rats. During the interval between two consecutive stimulations, evoked LFP corresponding to antidromic spikes and local activities are recorded in L2/3 and L5 regions of the M1. Application of bicuculline and CNQX, which respectively inhibit GABAergic and fast glutamatergic synaptic transmission, in L2/3, but not L5 of the M1 greatly reduces the local activity, but not the activity corresponding to antidrominc spikes induced by STN DBS to the same side.

By using c-fos expression as an indicator of neuronal activity, we find that the induction of PD decreases the number of c-fos-positive cells in the M1 region on the lesion side, and this number is brought back to the control level after being treated with STN DBS. Interestingly, this STN DBS-induced increase in c-fos-positive cells in the M1 region includes a population of large, intensively stained cells in the L5b region. Double fluorescence immunostaining indicates that these giant c-fos-positive cells are neurons (as positively stained by the antibody to NeuN), that most of them are of pyramidal–track (PT) type (as positively stained by the SMI32 antibody), and that they are not GABAergic in nature. Most of these giant c-fos-positive cells are back-labeled by Fast Blue dye that has been injected in the STN on the same side. The above anatomical results suggest that the majority of these giant c-fos-positive

neurons are corticospinal neurons. Further, these giant c-fos-positive cells are only found in the M1 on the lesion side of hemi-PD rats, but not in the M1 on the intact side of hemi-PD rats or in the M1 on either side of control rats after STN DBS. These observations suggest that some alterations in the local circuit on the lesion side of hemi-PD rats make the corticospinal neurons in this region more readily be stimulated by STN DBS. The altered neural circuit appears to involve GABAergic synaptic transmission because the appearance of these STN DBS-induced giant c-fos-positive cells is inhibited by local application of bicuculline in the M1 region.

Together, our results indicate that alterations in the local circuit involving both inhibitory interneurons and excitatory PT neurons residing in L2/3 and L5 occur in the M1 region of rats after the dopamine in the subtantia nigra pars compacta (SNpc) on the same side is depleted. The altered circuit may allows STN DBS to activate corticospinal neurons and other neurons connected to corticospinal neurons and then to ameliorate the movement disorders as resulting from the degeneration of dopamine neurons in the SNpc.